35 U.S.C. §112, First Paragraph (Enablement)

At pages 3-14 of the Office Action, claims 27-35 and 41-44 were rejected as allegedly containing "subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention."

Applicants respectfully traverse the rejection in light of the following comments.

There are several factors that must be considered when determining whether there is sufficient evidence to support a determination that a disclosure satisfies the enablement requirement. *In re Wands*, 858 F.2d 731 (Fed. Cir. 1988). These factors, often referred to as the "*Wands* factors," were reviewed by the Examiner in the present Office Action. The application of the *Wands* factors to the pending claims is addressed in sections (1)-(8) below.

(1) Breadth of the Claims

The first *Wands* inquiry requires a determination of exactly what subject matter is encompassed by the claims and how broad the claims are with respect to the disclosure. Subsequent inquiries (detailed in sections (2)-(8) below) determine if one skilled in the art, at the time the application was filed, was enabled to make and use the full scope of the claimed invention without undue experimentation. The relevant concern is whether the scope of enablement the disclosure (combined with the knowledge in the art) provides to one skilled in the art is commensurate with the scope of protection sought by the claim.

Independent claim 27 is directed to a method for activating T cells in a subject by administering to the subject an amount of a cytochrome P450 CYP1B1 sequence effective to activate T cells that recognize a CYP1B1 epitope. The sequence used in the claimed methods is thus limited both structurally (it must be a P450 CYP1B1 sequence) and functionally (it must be a sequence that is effective to activate T cells that recognize a CYP1B1 epitope).

(2) The Nature of the Invention

This *Wands* factor addresses the subject matter to which the claimed invention pertains. The nature of the invention is the backdrop for other *Wands* factors such as the "state of the art" ((3), below) and the "level of skill possessed by one of skill in the art" ((4), below).

The claimed methods generally relate to the use of a tumor associated antigen to activate T cells in a subject. The claimed invention is based, at least in part, upon applicants' discovery that CYP1B1 is expressed in a wide range of tumors but not in the normal tissues that were tested. As a result of its marked preferential expression of CYP1B1 in tumors, the specification teaches that CYP1B1 sequences can be used to immunize a subject, thereby resulting in activated T cells that recognize a CYP1B1 epitope and mediate an immune response against a CYP1B1-expressing tumor.

(3) State of the Prior Art

The state of the prior art is what one skilled in the art would have known, at the time the application was filed, about the subject matter of the claimed invention. The state of the art provides evidence for the degree of predictability in the art ((5), below) and is inversely related to both the amount of direction or guidance needed in the specification ((6), below) and the need for working examples in the specification ((7), below) to meet the enablement requirement.

At the time the present application was filed, methods of inducing an immune response in a subject were well known in the art. A copy of U.S. Patent No. 5,589,466 ("the '466 patent") is enclosed as evidence of the state of the art with respect to the use of nucleic acids to generate an immune response in a subject. The '466 patent provides extensive direction as to how to prepare a nucleic acid encoding an immunogen as well as how to administer the nucleic acid to a subject so that the immunogen is expressed *in vivo* and results in the induction of an immune response against the encoded antigen in the subject. The immunization methods described in the '466 patent are of general applicability and can be used with any nucleic acid sequence that is identified as having the necessary features of an immunogen. Furthermore, it is noted that the claims that issued in the '466 patent encompass the use of a DNA encoding *any* immunogen to

induce an immune response. In contrast, as detailed in section (1) above, the claims of the present application are limited to the use of a cytochrome P450 CYP1B1 sequence.

The Examiner cited several references in support of the assertion that gene therapy and cancer immunotherapy cannot be predictably performed.

The gene therapy references (Crystal and Verma) cited in the Office Action do not describe the use of a nucleic acid to induce an immune response against a protein encoded by the administered nucleic acid. Rather, proteins encoded by the nucleic acids described by these references were intended to be mediators of a biological response (see, e.g., the abstract of Verma describing the insertion of "corrective genetic material" into cells in an attempt to alleviate symptoms of disease).

The three references cited in the Office Action as relevant to cancer immunotherapy describe several obstacles that have been faced in the field. However, the general obstacles reviewed in those references do not negate the particular experimental findings of the present application that describe the usefulness of CYP1B1 as a target for immunization in cancer patients. In fact, the primary limitation of cancer immunotherapy cited by the Gouttefangeas reference was the lack of suitable antigens for many tumors. It is precisely this unmet need that is solved by the present application (which identifies CYP1B1 as a particularly useful target for immunotherapy).

(4) Relative Skill of those in the Art

This *Wands* factor refers to the skill of those in the art in relation to the subject matter to which the claimed invention pertains at the time the application was filed. The level of skill in the biological arts is generally considered to be high.

(5) Level of Predictability in the Art

The level of predictability in the art refers to the ability of one skilled in the art to extrapolate the disclosed or known results to the claimed invention. Accordingly, what is known in the art provides evidence as to the question of predictability.

As described in section (3) above and in the '466 patent, it was known in the art at the time the present application was filed that nucleic acids can be administered to a subject to generate an immune response in the subject against an immunogen encoded by the administered nucleic acid. Accordingly, one skilled in the art would have been able to readily extrapolate the findings disclosed in the present application (that CYP1B1 is preferentially expressed in tumors) to predict that administration to a subject of a nucleic acid encoding a protein that is preferentially expressed in tumors would result in the induction of an anti-tumor immune response in the subject.

(6) Amount of Direction Provided by the Inventor

The amount of guidance or direction refers to that information in the application, as originally filed, that teaches how to make or use the invention. The more that is known in the prior art ((3), above) about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is ((5), above), the less information needs to be explicitly stated in the specification. The specification need not disclose what is well-known to those skilled in the art and preferably omits that which is well-known and already available to the public.

The specification teaches that CYP1B1 sequences can be used to immunize a subject, thereby resulting in activated T cells that recognize a CYP1B1 epitope and mediate an immune response against a CYP1B1-expressing tumor. In view of the knowledge in the art with respect to immunization methods (including nucleic acid immunization as exemplified in the '466 patent), the direction contained in the application as filed was sufficient to permit, at the time the application was filed, the practice of the claimed methods without undue experimentation and with a reasonable expectation of success.

(7) Existence of Working Examples

While the presence of working examples in the specification can be helpful in establishing enablement, compliance with the enablement requirement does not turn on whether

a working example is disclosed. An applicant need not have actually reduced the invention to practice prior to filing a patent application. In general, the specification need not contain an example if the invention is otherwise disclosed in such manner that one skilled in the art will be able to practice it without undue experimentation.

The present application contains working examples demonstrating that CYP1B1 is expressed in a wide range of tumors but not in the normal tissues that were tested. Because of applicants' experimental findings clearly showing that CYP1B1 is expressed in many types of cancers, but not expressed in those normal tissues studied, the person of ordinary skill in the art at the time of filing of the present application would have reasonably expected that CYP1B1 sequences could be used to generate an immune response against CYP1B1-expressing tumor cells.

(8) Quantity of Experimentation Needed to Make or Use the Invention Based on the Content of the Disclosure

A considerable amount of experimentation is permissible, if it is merely routine, or if the specification provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed.

Because applicants have discovered a marked preferential expression of CYP1B1 in tumors and have disclosed in the specification that CYP1B1 sequences can be used to stimulate the immune system of cancer patients, it would require only routine preparation and experimentation for the person of ordinary skill to use such sequences to induce an immune response in a subject.

Conclusion

In view of the foregoing, applicants respectfully submit that the person of ordinary skill in the art, at the time the present application was filed, would have been able to follow the guidance provided in the specification and apply the relevant knowledge in the art so as to

practice the claimed methods without undue experimentation and with a reasonable expectation of success.

Applicants are in full agreement with the statement on page 11 of the Office Action that a claimed invention must be enabled at the time of filing of the application. The publication of Gribben et al. entitled "Unexpected Association Between Induction of Immunity to the Universal Tumor Antigen CYP1B1 (ZYC300) and Response to Next Therapy" ("Gribben") was submitted with the previous response merely to confirm that, as taught in the specification, CYP1B1 sequences can be used to generate an immune response against CYP1B1-expressing tumor cells. Consistent with the foregoing, section 2164.05 of the MPEP states that

> Applicant should be encouraged to provide any evidence to demonstrate that the disclosure enables the claimed invention... To overcome a *prima facie* case of lack of enablement, applicant must demonstrate by argument and/or evidence that the disclosure, as filed, would have enabled the claimed invention for one skilled in the art at the time of filing. This does not preclude applicant from providing a declaration after the filing date which demonstrates that the claimed invention works.

The publication of Gribben was not cited to establish the state of the art at the time of filing. Instead, it was provided as a demonstration that CYP1B1 sequences can be used effectively to stimulate an anti-CYP1B1 immune response and provide a clinical benefit to cancer patients. Even though Gribben did not describe a positive outcome in every patient to which a CYP1B1 sequence was administered, a compound undoubtedly need not be effective in *every* patient in order to have clinical utility. Many drugs are used clinically even though they are known to be effective in only a fraction of the patient population.

The Office Action (at the top of page 13) cited a passage from page 1 of Gribben to support an assertion that even as of today the state of the art with respect to cancer vaccines is unpredictable and additional experimentation is necessary. However, the passage cited in the Office Action was taken from the first paragraph of the introduction of Gribben. Immediately following the quoted passage, Gribben begins its review of the CYP1B1 literature (stating that "CYP1B1 protein is expressed in virtually all human tumors and little heterogeneity of expression is observed within individual tumors" and that expression of the protein in adult

normal tissues is rare). Gribben concludes the review of the CYP1B1 literature by stating that "these data suggest that CYP1B1 can function as a nearly universal tumor antigen and supported investigation of CYP1B1-directed vaccination for the treatment of human cancer." (Gribben at pages 1-2). The passage of Gribben cited in the Office Action was therefore not a conclusion, but was presented as a backdrop to the CYP1B1 studies that were conducted and described therein.

The Office Action (at the bottom of page 12) asserted that Gribben relies on critical features that were not disclosed in the specification nor taught in the prior art. In particular, the Office Action stated that Gribben describes the use of an inactivated CYP1B1 DNA formulated within biodegradable poly-DL-lactide-coglycolide microparticles. However, there is no evidence of record to suggest that these particular features are critical and that other CYP1B1 sequences (e.g., wild type CYP1B1) and other means of delivering DNA (e.g., administration of naked DNA) could not also be used to induce an immune response in a subject.

In summary, (i) the specification provides experimental findings that CYP1B1 would be a useful target for immunization in cancer patients, (ii) the skilled person at the time the present application was filed knew how to administer nucleic acids to a subject to generate an immune response, and (iii) the publication of Gribben confirms the result that is achieved when a CYP1B1 nucleic acid is administered to a human patient.

Accordingly, applicants respectfully submit that the claims satisfy the enablement requirement and therefore request that the Examiner withdraw the rejection of independent claim 27 and the claims that depend therefrom.

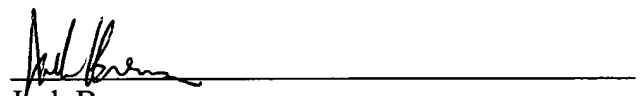
CONCLUSIONS

Applicants submit that all grounds for rejection have been overcome and that all claims are in condition for allowance, which action is requested.

Enclosed is a Petition for Three Month Extension of Time and a check for the Petition for Extension of Time fee. Please apply any other charges or credits to deposit account 06-1050, referencing Attorney Docket No. 12489-003002.

Respectfully submitted,

Date: April 18, 2006



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